UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,203	03/13/2002	Tracey Brown	650064.406USPC	8511

500 7590 10/30/2008

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/889,203	BROWN, TRACEY	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/19/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, amendment and remarks filed 08/19/2008. Claims 27, 28, 32-34, 38-40, 44-46, 50 and 51 are amended. New claims 53-56 are added. Claims 27-56 are pending.

Declaration:

The declaration filed 8/19/08 does not identify the rules under which it is filed. It appears that it is filed under 1.132 since applicant has not attempted to use the declaration to swear behind the references; and applicant is invited to make the correction in response to this office action. The merits of the declaration are discussed below.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 27, 33, 39 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Falk et al. (US 5,985,850).

Falk discloses injectable formulations comprising anti-cancer agent or chemotherapeutic agent and hyaluronic acid (column 10, lines 8-59). The preferred molecular weight for the hyaluronan is less than 750,000 Daltons (claims 142, 83, 84 and 92). The anti-cancer drug or chemotherapeutic agent of Falk, specifically, methotrexate and 5-fluorouracil (claims 38 and 79) meet the drug and/or anti-neoplastic agent requirement of the claims. The method of administration of the hyaluronan containing composition is by intravenous, intra arterially, intraperitoneally, intrapleurally, transdermally, topically, rectally, or by direct injection of the of the composition into a tumor (column 10, lines 48-55) and this administration meets the requirements of the method claims where the method step administers the composition. Since the method of claim 27, 33 and 39 administers the hyaluronan and drug composition to a patient to enhance the efficacy of a drug for a cancer cell, it flows that, when Falk administers the same composition to tumor site of a patient, the composition would inherently enhance the efficacy of the drug for cancer cell. Applicant's declaration, as previously noted, is not commensurate with 750 kDa. Thus, the demonstration provided in applicant's declaration has no data at the lower end of 750 kDa and the 30 kDa data is much lower than 750 kDa. Therefore, there is no conclusive factual evidence that molecular weight equal to 750,000 Dalton provides unusual and unexpected results. Therefore, the evidence provided does not support hyaluronic acid having molecular weight of equal to 750,000 Daltons as being inventive over the disclosure in the prior art of a molecular weight of less than 750,000. Falk anticipates the claims. However, in the, alternate, since Falk does not explicitly state that efficacy of a drug for a cancer cell is enhanced by administering a composition containing hyaluronan and anti-neoplastic agent or cytotoxic agent, it would be expected that the administration of the composition containing hyaluronan and anti-neoplastic agent or cytotoxic agent to a patient as described by Falk would provide the effect

recited in the claims thereby rendering obvious the effect of enhancing the efficacy of a drug for cancer cell. It is noted that a range of molecular weight is recited indicating that one can use the hyaluronic acid having an optimum molecular weight for the desired goal. Furthermore, a molecular weight of recited molecular weight range at the lower limit of 400,000 Da is less than 750,000 Da so that the less than 750,000 Da for the HA meets the requirements of the claims.

Response to Arguments

3. Applicant's arguments filed 8/19/08 as it relates to the current rejection have been fully considered but they are not persuasive. It is noted that the claims have been amended but the molecular weight of the HA in claims 27, 33, 39 and 45 is at a molecular weight of 400,000 to 900,000 Da.

Applicant argues that Falk does not inherently teach or explicitly teach that the HA can be utilized to enhance the efficacy of a chemotherapeutic agent, that inherency cannot be based on probabilities and possibilities and that the examiner provided no extrinsic evidence for rejections. This argument is not persuasive. The method of enhancing the efficacy of chemotherapeutic agent in the invention involves administering hyaluronic acid to a subject. In the same way, when the HA is administered in the prior art, it would inherently enhance the efficacy of the therapeutic agent. The fact that administration of HA to a subject in the claims and in the prior enhances the efficacy of the therapeutic agent is not based on possibilities and probabilities art. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

4. Applicant also argues that evidence of record suggests that HA having molecular weights of less that 400,000 Da are structurally different from those having higher molecular weights.

This argument is not persuasive because the prior art does not use HA of less than 400,000. The PTO relies on the prior to in the determination of patentable subject matter and since the PTO does not have any laboratories, the burden falls on applicant to provide persuasive evidence once a rejection is made and to provide in this case why administration of HA having molecular weight in the range recited would not enhance the efficacy of the therapeutic agent. Examiner provided all the requisite reasons to show that the prior art that administers HA just as in the claims would inherently enhance the efficacy of therapeutic agents. Regarding exemplification or not in the prior art, it is noted that a prior art reference is not limited by its working examples, rather that the reference must be evaluated for what it teaches.

5. Applicant further argues that HA having molecular weight of more than 400,000 Da as claimed do not facilitate tissue penetration. Applicant appears to be using molecular weight of HA that is not in the rejection for Falk and it is unclear as to why the applicant is insisting that the molecular weight of HA in Falk is less than 400,000 when Falk discloses using less than 750,000; 150,000 and 225,000 are not the only molecular weight that is less than 750,000. Furthermore, claims 27, 33 and 39 recite a range of 400,000 to 900,000 Da and the molecular weight of Falk falls within the range. Therefore, Falk anticipates claims 27, 33 and 39.

6. Regarding the obviousness rejection, applicant's argument that the examiner failed to provide prima facie case of obviousness is not persuasive because, Falk is an anticipatory reference and in the alternate, renders obvious the claims as it relates to explicit narration of enhancing the efficacy of the therapeutic agent. The obviousness was not a modification of the molecular weight but that since the claimed invention and the prior art administer HA, it is prima facie that the administered HA would provide enhancement of the therapeutic agent. Applicant

has not provided contrary evidence that the administration of HA in the prior art fails to enhance the efficacy. The burden shifted to applicant to provide evidence to the contrary.

7. Applicant appears to be requiring factual evidence from the examiner. But the PTO does not have laboratories and applicant has provided no evidence to the contrary the HA of Falk cannot enhance the efficacy of the active agent when administered.

8. Applicant argues that Falk has deficiencies. The examiner disagrees. Falk does not have deficiencies with respect to claims 27, 33 and 39. The declaration of Dr. T. Brown will be addressed below.

9. Claims 27, 33, 39 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by della Valle et al. (US 5,442,053) for reasons of record and reiterated herein below.

10. della Valle describes an embodiment in which a pharmaceutical composition comprising active agents and hyaluronic acid as the carrier vehicle (abstract) for administration in various forms (column 3, lines 60 and 61; column 5, line 60; column 14, line 13; column 16, lines 38-46; column17, line 11). The cytotoxic agents named in della Valle are fluorouracil, methotrexate and podophyllin (column 24, lines 65 and 66) meeting the requirements of claims 27, 32, 33, 38, 44 and 50. Hyaluronic acid having molecular weight of from between 300,000 and 730,000 Da is used (claims 5, 8, 18 and 32) meeting the requirements of claims 27, 28, 33, 34 and 40. The administering of the composition comprising the HA and the cytotoxic agents meets the administration limitation of the method steps of the claims.

Response to Arguments

11. Applicant's arguments filed 8/19/08 have been fully considered but they are not persuasive.

12. Applicant's main argument is that de Valle is deficient because the reference failed to explicitly say that HA enhances efficacy of chemotherapeutic agent. But the claimed invention enhances the efficacy of chemotherapeutic agent by administering HA and chemotherapeutic agent. The prior art also administers chemotherapeutic agent and HA, with the HA having molecular weight within the recited molecular weight. There is thus no deficiency in de Valle and applicant has not provided factual evidence that the administration of HA and chemotherapeutic agent to a subject enhances the efficacy while the administration of HA and chemotherapeutic agent in the prior art cannot enhance the efficacy. Applicant's argument is not persuasive that same process using same product should provide different results.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 27-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over della Valle et al. (US 5,442,053) according to the rejections of record and modified to account for the amendment to claims 28, 34, 40, 46 and new claims 53-56.

15. della Valle is discussed above and has been shown to anticipate claims 27, 33, 39 and 45 in which the molecular weight of hayluronic acid is 400,000 to 900,000 Da. della Valle does not use hyaluronic acid having molecular weight of claims 28-31, 34-37, 40-43, 46-49, 51, 52 and including new claims 53-56. However, the disclosure to use hyaluronic having a range of molecular weight or from about 500,00 to about 730,000 Da (claims 5, 8, 18 and 32), and the

general teaching that as a vehicle, hyaluronic acid of varying molecular weights can be used (column 18, lines 63-66), suggest that although, molecular weight in the range of about 500,000 to 730,000 Da may be used, hyaluronic acid of other molecular weight may also be used including hyaluronic acid of molecular weight higher than 730,000 Da being mindful of the intrinsic viscosity of the hyaluronic acid carrier vehicle (column 4, lines 13-23). Therefore, taking the general teaching of della Valle, the person of ordinary skill in the art at the time the invention was made would have reasonable expectation of success that using hyaluronic acid having molecular weights in a range that is higher than the 730,000 Da that results in a carrier vehicle having desired viscosity would provide the anticipated therapeutic composition for successful delivery of cytotoxic agents.

Response to Arguments

16. Applicant's arguments filed 8/19/08 have been fully considered but they are not persuasive.

17. Applicant argues that the examiner has not provided the requisite motivation to modify the teachings of della Valle to use hyaluronan having molecular weight greater than 750,000. The examiner disagrees. The rejection was clear in pointing to the applicant that della Valle provides a general teaching that as a vehicle, hyaluronic acid of varying molecular weights can be used (column 18, lines 63-66), suggest that although, molecular weight in the range of about 500,000 to 730,000 Da may be used, hyaluronic acid of other molecular weight may also be used including hyaluronic acid of molecular weight higher than 730,000 Da being mindful of the intrinsic viscosity of the hyaluronic acid carrier vehicle (column 4, lines 13-23). Therefore, the suggestion that hyaluronic acid having molecular weight greater than 730,000 Da can be used

provides the motivation to employ hyaluroniuc acid having molecular weight that is greater than 750,000.

18. Applicant argues that della Valle does not teach that therapeutic administration of hayluronic having molecular weight equal to or greater than 750,000 would enhance the efficacy of a chemotherapeutic agent. The examiner disagrees and is note worthy that the applicant appears to suggest that at best hyaluronic acid having molecular weight of below 730,000 Da is what is taught by della Valle; and this is the reason for rejecting claims 27, 33, 39 and 45 under 35 USC 102(b). However, della Valle suggests the use of hyaluroniuc acid having molecular weight of greater than 730,000 Da such that the ordinary skilled artisan would reasonably expect that hyaluroniuc acid having molecular weights greater than 730,000 would be applicable in della Valle, thereby rending claims 28-31, 34-37, 40-43, 46-49, 51, 52 and new claims 53-56 and does dependent therefrom obvious. The expectation of the ordinary skilled artisan to use hyaluronic acid having molecular weight of greater than 730,000 is not a conclusory assertion as applicant concludes because della Valle suggests the use of greater than 730,000 Da.

19. Applicant also argues that the declaration of Dr. T. Brown provides evidence that the ordinary person would have failed to expect higher molecular weight hyaluronan based composition to provide desirable viscosity for systemic administration since viscosity increases with molecular weight. This is not persuasive because applicant appears to say that the viscosity of hyaluronic acid or other compounds is dependent only on the molecular weight. On the contrary, viscosity is dependent both on the concentration and molecular weight of the polymers of interest as evidenced by claim 16 of US 4,665,107 and lines 24-35 of column 28 of US 7,420,033. Therefore, della Valle renders obvious the use of hyaluronic acid having molecular weight of greater than 730,000 Da.

Declaration by Dr. Tracy Brown:

20. The declaration under 37 CFR 1.132 filed 8/19/08 is insufficient to overcome the rejection of claims 27, 33, 39 and 45 based upon the rejection under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Falk et al. (US 5,985,850).35 U.S.C. 103(a) as set forth in the last Office action because: The declaration in 1B uses molecular weight of about 150 kDa for the HA, 250, 400 and 700 kDa in Figs 2, while claims 27, 33, 39 and 39 use molecular weight range of 400-900 kDa. The attempt of the declaration to argue against 250, 400 and 700 kDa in an effort to overcome the Falk reference is not persuasive because the claims 27, 33, 39 and 45 include HA having those molecular weights and because 250, 400 and 700 kDa are less than 750 kDa, Falk meets the limitation for those molecular weights. Paragraphs 7 and 8 of the declaration do not use amounts of HA and drugs and it is not persuasive that compositions can be prepared without using any amounts and it is also not persuasive that a composition prepared by dumping together HA and drug in any amounts would provide the desired effect. If that were the case, then the declaration would also apply to the prior art.

21. The declaration under 37 CFR 1.132 filed 8/19/08 is insufficient to overcome the rejection of claims 27-56 based upon the rejections under 35 U.S.C. 103(a) as being unpatentable over della Valle et al. (US 5,442,053) as set forth in the last Office action and modified to accommodate the amendment because: The declaration specifically mentions the Falk reference, US 5,985,850 ands not the della Valle reference. It is therefore unclear how the examiner can address opinion that is generated for the Falk reference as if it were for della Valle. However, the examiner agrees with paragraph 8 of the declaration that viscosity increases with molecular weight but the declaration, being an opinion declaration has not accounted for the effect of

concentration on the viscosity. Regarding the phase I and II clinical trials presented in the declaration, it is noted that only the molecular weight of the HA and the drugs are named, there are no amounts/concentrations of HA or the drugs and it is fair to assume that data cannot be generated without specific concentrations of the HA and the drug because such a test would mean the dumping of any amount of HA and drug to form a composition that may provide any effect of any desired treatment, which by implication would cover the prior art.

No claim is allowed.

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 7571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Blessing M. Fubara/
Examiner, Art Unit 1618